

Properties and Actions of Bridged Diphenyl Acaricides

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The properties and actions of the bridged diphenyl acaricides are discussed. These pesticides, which are more or less structurally related to DDT, were the first of the specific acaricides to be developed. They exhibit remarkable properties of specificity, being primarily toxic to phytophagous mites but of very low toxicity to most nontarget species, including insects, fish, birds, and mammals. Although many important facets of their broad mode of action are understood, virtually nothing is known of their primary mode of action or the underlying bases of their specificities. In most ways they are model compounds for integrated control and pest management activities and thus merit greater attention than they have received to elucidate the fundamentals underlying their unusual properties and actions.

Introduction

Those pesticides which are primarily effective against the order Acarina, particularly phytophagous mites, at dosages which are largely ineffective against insects are designated as specific acaricides to distinguish them from organophosphorus and carbamate insecticides, which possess both acaricidal and insecticidal activities. The specific acaricides exhibit remarkable properties of specificity. In most ways they are model compounds for integrated control and pest management activities and thus consideration of their properties and actions merits attention in this Conference on Human Health Effects of New Approaches to Insect Pest Control.

The order Acarina—mites and ticks—comprises over 20,000 species and includes many important pests of both plants and animals. Although there is virtually no crop without mite pests, phytophagous mites were decidedly of secondary importance as pests in orchard and field 40 to 50 years ago. But mite problems were accentuated with the advent of modern pesticides and agricultural practices, and for the past few decades phytophagous mites as a

group have been rated among our most serious pests (1). DDT and the other early developed chlorinated-hydrocarbon insecticides were found to be essentially ineffective against phytophagous mites. Not only were they ineffective, but their application for insect control resulted in the increase of mite and aphid populations to serious pest status. Subsequently, similar effects arose with the introduction of certain organophosphorus and carbamate insecticides. Such outbreaks of secondary pests apparently result from a complex of causes and direct effects of the pesticides on predators, host plant physiology (nutrition), and pest fecundity and altered agricultural management practices have all apparently played a part (2-5).

The ineffectiveness of the chlorinated-hydrocarbon insecticides in controlling the various phytophagous mites, together with the increase in mite populations following their use for insect control, stimulated and continues to fuel active search for compounds effective for mite control. The following discussion concerns those specific acaricides more or less structurally related to DDT—the bridged diphenyl acaricides—which were the first of the specific acaricides to be developed. Interest in such compounds and their chemical structural requirements arose because of the early identification of certain of these compounds which exhibited effective acaricidal action.

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The effectiveness of benzyl benzoate for medicinal use in the treatment of scabies (itch mite) had been known since the late 1930's (6), and its use for impregnation of clothing for control of chiggers transmitting scrub typhus was developed for use in the Pacific in World War II (7). Ring-chlorinated analogs of benzyl benzoate and phenyl benzoate were shown in the late 1940's to be active acaricides against phytophagous mites (8), but they were not useful in the field because of unfavorable phytotoxic properties. Azobenzene, which was developed by Blauvelt in 1945 against greenhouse mite pests, was the first of the bridged diphenyl compounds to be practically used against phytophagous mites (9). The striking acaricidal activity of two additional compounds, even more closely related to DDT than benzyl benzoate or azobenzene, were also reported about this same time. The first was bis(*p*-chlorophenoxy)methane (Neotran), which was patented by Dow Chemical Co., Midland, Michigan in 1943 and whose activity against the citrus red mite was reported by Jeppson in 1946 (10). The second was bis(*p*-chlorophenyl)methylcarbinol (chlorfenethol), which was patented by Sherwin-Williams Co., Pittsburgh, Pa. in 1947 and whose acaricidal activity was reported by Grummitt in 1950 (11). Investigations by Metcalf (12) and Eaton and Davies (13) into the chemical structural requirements for acaricidal activity with these forerunner compounds as models for additional compounds, revealed that the bridging group between the two phenyl rings was the critical structural component responsible for determining insecticidal versus acaricidal activity. A number of active acaricidal compounds containing two phenyl groups, with and without chlorine substituents and linked by suitable bridging structures including $-OCH_2O-$, $-CH_2O-$, $-CH_2S-$, $>CH(OH)CH_3$, $-OSO_2$, $-O-C=O$, $-O-COO-$, $-SO_2-$, $-N=N-$, $O-N=N-$, $-NH-NH-$, $>N-NO$, $-CH=CH-C=O$, $-S-$, $-O-$, and $-CH_2-$, and a number of structural requirements for acaricidal activity were identified in these two pioneering studies.

Current Diphenyl Acaricides

From the beginnings described above a number of acaricides of the bridged diphenyl structure have been developed. In considering the currently available commercial acaricides it must be remembered that these compounds are the end products of extended and multiple selection processes and that many other compounds have been evaluated in course, some even to the point of being produced commercially and then discontinued. It must also

be remembered that these commercial products are selected for many characteristics in addition to innate acaricidal toxicity, including field performance, toxicology, plant tolerance, compatibility, formulation and storage, post-harvest residues, production, and economics.

Diphenyl Carbinols

An important group of commercial acaricides is the diphenyl carbinol group of which chlorfenethol was the first member. Chlorobenzilate (ethyl 4, 4'-dichlorobenzilate) was introduced in 1952 by J. R. Geigy S. A., Basle, Switzerland (14). The isopropyl ester, chloropropylate (isopropyl 4,4'-dichlorobenzilate), was initially evaluated at this same time but not developed until the 1960's, when its re-evaluation demonstrated that it provided longer residual control of organophosphorus-resistant mites than did chlorobenzilate (15).

The phenomenon of resistance in mites to specific acaricides, as well as acaricidal organophosphorus and carbamate insecticides, is as severe or even more so than insecticide resistance in any group of insects. There is hardly any group of acaricides to which the versatile mites have not responded by the development of resistance (16). Typical cross and multiple resistance patterns to the different groups of acaricides have appeared among various mite species (17). The phenomenon of resistance is the second, and undoubtedly most important, factor responsible for the continuing active search for new acaricides.

A third member of the carbinol series, bromopropylate (isopropyl 4,4'-dibromobenzilate) was introduced by J. R. Geigy S. A. in the 1970's; it was found to be more effective than chloropropylate on resistant mite strains and also showed longer residual activity and improved plant tolerance. The significance of the carbinol bridging group to specific acaricidal activity is particularly indicated by the commercial development of the carbinol analog of DDT, dicofol [4,4'-dichloro- α -(trichloromethyl)-benzhydrol], by the Rohm and Haas Co., Philadelphia, Pa. in 1955. It is somewhat surprising that this compound was not developed until such a long time after the activity of chlorfenethol was discovered. A final carbinol is the recently introduced proclonol [bis(*p*-chlorophenyl)cyclopropylcarbinol] (Jansen Pharmaceutica N.V., Belgium and Sankyo Company Ltd., Tokyo, Japan). Since proclonol does not contain the trichloromethyl group of dicofol or the ester groups of chlorobenzilate, chloropropylate, and bromopropylate, it is a more stable molecule under potentially degradative conditions (18,19).

Diphenyl Sulfones, Sulfides, and Sulfonates

Eaton and Davies (13) found that diphenyl sulfone was an active acaricide but it was adversely phytotoxic. *p*-Chlorophenyl phenyl sulfone was also active, but bis(*p*-chlorophenyl)sulfone was less active. The former compound was one of the active ingredients of Sulphenone, at one time produced by Stauffer Chemical Co. Later investigators found that additional chlorination restored acaricidal activity and essentially eliminated phytotoxicity resulting in the development of tetradifon (*p*-chlorophenyl 2,4,5-trichlorophenyl sulfone) by Philips-Duphar B.V., Amsterdam, Holland, as also was tetrasul (*p*-chlorophenyl 2,4,5-trichlorophenyl sulfide) which is less residual on foliage but more active on mite winter eggs due to greater penetration of the sulfide than the sulfone (20,21). The same tetrachloro ring substitution produces an active compound with an azosulfide bridging group in chlorfensulfide, $\{[(p\text{-chlorophenyl})\text{thio}][2,4,5\text{-trichlorophenyl}]\text{diimide}\}$, a product of Nippon Soda Co., Ltd., Tokyo, Japan, which is usually formulated with chlorfenethol or Neotran and DDDS [bis(*p*-chlorophenyl) disulfide]. Discovery of the acaricidal properties of the chlorinated phenyl benzene sulfonates in the late 1940's (22,23) resulted in the development of ovex (*p*-chlorophenyl *p*-chlorobenzenesulfonate) by the Dow Chemical Co. and fenson (*p*-chlorophenyl benzenesulfonate) by the Boots Co., Ltd., Nottingham, England.

New Compounds

Active search still continues for acaricidally active compounds more or less related to the bridged diphenyl structure. Several series of acid chloride phenylhydrazones have been shown to have acaricidal activity; one of these, benzoyl chloride (2,4,6-trichlorophenyl) hydrazone (Banamite) is being developed by the Upjohn Co., Kalamazoo, Michigan, for the control of mites attacking citrus (24,25). Another new class of acaricidally active compounds, esters of 3-hydroxy-2-arylindones, has been identified by investigators of the Union Carbide Corp., South Charleston, West Virginia, and one, 3-(pivaloyloxy)-2-(2,4,6-trimethylphenyl)-indone (UC-41305) has shown sufficient promise to merit extensive field testing (26). A third new class of compounds showing activity against both mites and ticks is the 1,5-phenyl-substituted 1,3,5-triazapenta-1,4-dienes under development by The Boots Co. The most active compound to both mites and

ticks, 1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene (amitraz) is undergoing world-wide testing (27,28).

Biological Activity and Specificity

The specific acaricides have been defined as pesticides which are primarily effective against members of the order Acarina, particularly phytophagous mites, at dosages which are largely ineffective against insects. In general, this is a satisfactory broad definition but it is also one to which there are a number of qualifications.

Insecticidal Activity of Acaricides

As a group, the specific acaricides can be considered to be of relatively low toxicity to insects at dosages affecting mites. However, there are examples of toxicity to insects. Ovex, *p*-chlorophenyl *p*-chlorobenzyl ether, and bis(*p*-chlorophenyl) sulfide, sulfoxide, sulfone, and ether have been shown to be active as stomach poisons to clothes moth larvae (29). The same toxicity relationships to Mexican bean beetle larvae and eggs and adults of the two-spotted spider mite have been demonstrated among a series of substituted bisphenoxy-methanes and phenylbenzene sulfonates (22,30). Metcalf has shown (12) that selected changes in the aliphatic portion of the DDT molecule can produce a series of compounds of intergrading insecticidal to acaricidal activities.

The low toxicity of the specific acaricides to insects is of practical importance since they present relatively little toxic hazard to beneficial insects. Anderson and Atkins classify chlorobenzilate, chlorfenethol, dicofol, fenson, Neotran, ovex, and tetradifon as relatively nontoxic to the honey bee (31). In fact, the direct control of acarine disease of bees has been accomplished with chlorobenzilate, chlorfenethol, and ovex (32). The specific acaricides also have generally been shown to be practically nontoxic to entomophagous insects (33-36). Their low toxicity to insects and warm-blooded animals has facilitated the control of parasitic mites in insect and laboratory animal colonies (37,38).

Acaricidal Specificity

The specificity of acaricides is not limited to differential toxicity between mites and insects for there are many examples of clearcut specificity in

relation to acaricidal activity itself. Most of the specific acaricides of the bridged diphenyl group including chlorfenethol, ovex, fenon, tetradifon, tetrasul, and chlorfensulfide, were developed on the basis of effectiveness against mites of the family Tetranychidae, e.g., European red mite, citrus red mite, two-spotted mite, Pacific mite, McDaniel mite, etc. These acaricides are not effective against mites of the family Tarsonemidae, e.g., cyclamen mite; family Eriophyidae e.g. citrus bud mite, citrus rust mite, tomato russet mite, and pear leaf blister mite; or family Tenuipalpidae, e.g., citrus flat mite. In fact, the normal recommended control chemicals for these mites were chlorinated hydrocarbon insecticides e.g., DDT and chlordane for the citrus bud mite and toxaphene, endrin, and endosulfan for the cyclamen mite and tomato russet mite. However, dicofol, chlorobenzilate, chloropropylate, bromopropylate, and proclonol are effective against mites of these families. Of practical importance to integrated control programs is the finding that many of the bridged diphenyl acaricides are less toxic to predaceous mites of the family Phytoseidae than to phytophagous mites (34,36, 39,40). The usual recommendations for control of parasitic mites and ticks suggest insecticides rather than specific acaricides. However, some of the specific acaricides have been shown to be active against parasitic mites and ticks, e.g., chlorobenzilate on harvest mites; Neotran, ovex, and Sulphenone on the northern fowl mite; Neotran on the swine mange mite, chlorobenzilate and dicofol on the fowl tick; and ovex and dicofol on cattle ticks.

Acaricidal and Fungicidal Activity

The far-reaching interrelationships of biological activity are well demonstrated by the combined acaricidal-fungicidal activity of most metal carbamate and nitrophenyl fungicides. Of the bridged diphenyl acaricides only ovex is reported to have fungicidal activity against powdery mildews but many of the other specific acaricides are fungicides as well as acaricides. Some of the new fungicides, e.g., benomyl (41) and herbicides, e.g., dalapon (42) also have acaricidal properties.

Mammalian Toxicity

The bridged diphenyl acaricides also maintain their remarkable properties of specificity with respect to mammalian toxicity, which is of particular interest to this conference (see Table 1). Their acute oral toxicities to laboratory animals are

among the lowest reported for insecticides-acaricides, the acute oral LD₅₀ values being ten or more times that of DDT. Acute dermal toxicities are also low but for dermal exposure the differential in toxicity to DDT found for oral exposure is not universally maintained, and in one case dicofol, dermal toxicity is slightly greater than that of DDT. Chronic oral no-effect levels show about the same differential to DDT for chronic oral toxicity as do the acute oral LD₅₀ values. However the chronic oral no-effect levels appear to be somewhat lower than one might anticipate from the acute oral LD₅₀ based on the translation that a daily dose of 40 ppm in the diet of the rat is equivalent to about 2.5 mg/kg-day.

One toxicological factor favoring the diphenyl carbinol acaricides is that storage levels in the tissues are not materially magnified from the levels in the diet. In the rat, DDT levels in the tissues are magnified from those in the diet 10- to 20-fold in the female and 5- to 10-fold in the male, whereas comparable values for dicofol are 1.5 in the female and 0.5 in the male and for proclonol they are 1 in the female and 0.25 in the male (19).

Toxicity to Nontarget Species

From the standpoint of environmental hazard, the bridged diphenyl acaricides also generally appear to maintain their properties of specificity with respect to toxicity to representative nontarget species (see Table 2). However, the acute oral toxicity of dicofol is relatively close to that of DDT for birds, though a large specificity differential is maintained by tetradifon. All of the acaricides reported in Table 2 are much less acutely toxic to fish and arthropods than is DDT. Nevertheless, on the basis of comparison of the chronic oral toxicities to acute oral toxicities reported for mammals, information on chronic toxicities to nontarget species would appear to be of interest.

The data reported here for toxicity to both mammals and nontarget species is minimal and incomplete. It tends to lead one to overconclude low toxicity and specificity of the bridged diphenyl acaricides. Much of the information on specific acaricides, particularly in relation to chemical structure-activity and toxicology is not to be found in the open literature but remains in industry- or government-controlled reports and files. It would be very useful if such information were reviewed, summarized, and made available in the open literature before it is essentially irretrievable. The recent review for chlorobenzilate and chloropropylate (15) is an example of what might be done.

Table 1. Mammalian toxicity of the bridged diphenyl acaricides^a

Compound	Acute oral LD ₅₀ mg/kg	Acute dermal LD ₅₀ mg/kg	Chronic oral no-effect level, ppm diet
DDT	87-500 150-400 (M) 250-400 (Rb)	1931-3263 2820 (Rb)	1-5 400 (D)
Chlorobenzilate	700-3200 729-4850 (M)	> 10,200 1000-3000 (Rb)	125 > 500 (D)
Chloropropylate	> 5000-34,600	> 150 > 10,200 (Rb)	40 300 (D)
Bromopropylate	5000	> 10,000 (Rb)	
Dicofol	575-1331 1810 (Rb) > 4000 (D)	100-1230 2100 (Rb)	20-100 300 (D)
Proclonol	3420 (M)		25 12 (M)
Tetradifon	> 5000-14,700 2000 (D)	> 1000 (Rb)	300 500 (D)
Tetrasul	3960-17,100 3440-14,700 (M)	> 2000 (Rb)	> 20
Chlorfensulfide	> 3000 (M)		50
Overex	2000-2050		25
Fenson	1560-1740	> 2000 (Rb)	

^aData from Kenaga and End (43), except for proclonol (19). All data are for the white rat unless otherwise coded; white mouse = M, rabbit = Rb, and dog = D.

Table 2. Toxicity of the bridged diphenyl acaricides to nontarget species^a

Compound	Birds		Fish		Arthropods	
		Acute oral LC ₅₀ , ppm diet		Acute LC ₅₀ , ppm water		Acute LC ₅₀ , ppm water
DDT	mallard	850-1200	rainbow trout	0.007	stonefly	0.016
	pheasant	300-700	blue gill	0.008	waterflea	0.002
	bob white	600-1000				
Chlorobenzilate			rainbow trout	0.6	waterflea	0.87
Chloropropylate			blue gill	1.8		
			rainbow trout	0.045		
Dicofol			blue gill	0.066		
	mallard	1700-1900	rainbow trout	100	stonefly	3000
	pheasant	2100-2300			waterflea	390
Overex	bob white	2800-3000				
Tetradifon			blue gill	0.7	stonefly	1.5
	mallard	> 5000	blue gill	1.1	amphipod	0.14
	pheasant	> 5000				

^aData from Pimental (44), except for chlorobenzilate and chloropropylate on fish (15).

Action of Bridged Diphenyl Acaricides

With the many examples of the remarkable properties of specificity of the bridged diphenyl acaricides, one would expect that there would be a number of clues to their primary mode of action and the underlying bases of specificity. In actuality, virtually nothing is known of the systems in mites which they affect. There is also very little experimental evidence by which to explain whether the lack of or low toxicity to insects is due to the absence of such systems or to other factors such as penetration, metabolism, elimination, etc. Likewise there is a comparable lack of evidence to explain other specificities among mites, ticks, fungi, and vertebrates. What information we have comes from relatively few studies, most of them on metabolism and concerned more with terminal residues than with primary mode of action.

Metabolism of Bridged Diphenyl Acaricides

Ovex: The first report on the metabolism of one of the bridged diphenyl acaricides was by Tomizawa in 1960 with ovex (45). Ovex was essentially not metabolized by eggs and adults of the citrus red mite but when injected into the abdomen of the American cockroach it was extensively hydrolyzed to *p*-chlorobenzenesulfonic acid, tissue titers of which increased in order of abdomen, mid gut, and excreta. These initial results suggested that lack of toxicity of ovex to the American cockroach might be accounted for by metabolic detoxication.

Dicofol: Initial studies on the metabolism of dicofol were related to its identification in the fruit fly in 1959 as an oxidative hydroxylation metabolite of DDT (46). In investigations on the fate of DDT in *Triatoma infestans*, Agosin and co-workers found that DDT was metabolized to DDE, dicofol, and a third chlorform-soluble metabolite (47). Dicofol was also metabolized to this same metabolite which co-chromatographed with di-*p*-chlorobenzhydrol (DBH). This identification was uncertain, however, since the metabolite was not converted to di-*p*-chlorobenzophenone (DCB) by chromic acid oxidation. Brown et al., in studies on the storage, distribution, and metabolism of dicofol in the rat found DDE, DCB, and DBH as metabolites (48). The highest tissue residues were in the body fat, with levels of intact dicofol greater than those of DCB which were greater than those of DDE. Principal excretion was in the feces, with

levels of dicofol greater than DDE greater than DCB. The metabolism of dicofol has also been investigated in susceptible (S) and dicofol-resistant (R) strains of the citrus red mite by Tabata and Saito (49). About 85% of the dicofol absorbed into S-mites was not metabolized, whereas only about 30% of the absorbed dose was found as dicofol in R-mites. No other chloroform-soluble compounds were detected in the mites. About 20% of the absorbed dicofol was recovered in R-mites as unidentified, but not DBH, water-soluble metabolites. These studies suggest that dicofol metabolism may be similar in the insect and mammal, though intermediate steps and reactions are not resolved, and that mite resistance to dicofol might be accounted for by metabolic detoxication, but by a different pathway than metabolism in the insect and mammal.

Chlorobenzilate, Chloropropylate, and Bromopropylate: Miyazaki et al. (50) examined the metabolism of chlorobenzilate and chloropropylate in over 300 microbial cultures and found that the most extensive metabolism was by a yeast, *Rhodotorula gracilis*, to di-*p*-chlorobenzilic acid (DBA), di-*p*-chlorobenzophenone (DCB), and several additional unidentified metabolites. Chlorobenzilate was more susceptible to hydrolysis than chloropropylate by carboxylesterases. Knowles and Ahmad investigated the metabolism of all three carbinols by rat liver preparations and proposed a metabolism pathway to the halo-substituted benzilic acid, benzhydrol, benzophenone, and benzoic acid with four or more additional but unidentified water-soluble metabolites (51). The limiting reaction was cleavage of the ester linkage by carboxylesterases which showed greater activity for the ethyl ester of chlorobenzilate than for the isopropyl ester of chloropropylate or bromopropylate. The halobenzoic acid was the primary metabolite for all three compounds. St. John and Lisk (52) studied the elimination and metabolism of chloropropylate in the dairy cow. The major elimination pathway was in the urine (in contrast to in the feces for dicofol noted above), where 28% and 55% of the dose were eliminated respectively as DBA and its conjugates. In the feces, approximately 6% was excreted intact and 5% as DBA. Secretion in the milk was a minor pathway, 0.11% as intact chloropropylate. Investigation of the comparative metabolism of chloropropylate and bromopropylate in the two-spotted mite and house fly by El Rubae and Knowles tentatively identified the same metabolic pathways as in rat liver (53). Although

some differences in penetration and metabolism were detected between spider mites and house flies, they were not substantial enough to account for the marked specificity of the two acaricides. Thus these studies provide no evidence that differences in metabolic pathways or metabolic detoxication account for the specificity of these three related compounds. They do suggest, however, that since ester hydrolysis is the limiting reaction and that the ethyl ester of chlorobenzilate is hydrolyzed by the carboxylesterases at a greater rate than the isopropyl ester of chloropropylate or bromopropylate, that the greater effectiveness of the isopropyl esters to resistant mites may be due to differences in detoxication by ester hydrolysis.

Banamite: The *in vivo* and *in vitro* metabolism of the experimental acaricide, Banamite, has been investigated in the two-spotted mite by Knowles and Aziz (54). They proposed that Banamite initially forms an unstable enol derivative by replacement of the benzoyl chlorine with hydroxyl. The enol derivative is converted to benzaldehyde 2-(2,4,6-trichlorophenyl)hydrazone (BATH) and benzoic acid 2-(2,4,6-trichlorophenyl)hydrazide (BOTH), the two major metabolites. Minor metabolites are produced by conversion of BATH to 2,4,5-trichloroaniline and benzaldoxime and of BOTH to 2,4,6-trichlorophenylhydrazine and benzoic acid. Eight additional but unidentified metabolites were also found.

Miscellaneous Actions of Bridged Diphenyl Acaricides

A number of miscellaneous actions on biological systems by the bridged diphenyl acaricides have been identified. Ovex, tetradifon, and dicofol have been shown to be inducers of mixed function oxidase reactions in mammalian systems, in fact ovex is more active than DDT in this regard (55-57). A number of the bridged diphenyl acaricides are inhibitors of ATPases in fish, insect, and mite tissues. Chlorfenethol, chlorobenzilate, ovex, chlorbenside (*p*-chlorophenyl *p*-chlorobenzene sulfide), Genite (2,4-dichlorophenyl benzenesulfonate), and particularly tetradifon are inhibitors of mitochondrial oligomycin-sensitive Mg^{2+} -dependent ATPase and relatively ineffective against oligomycin-insensitive Mg^{2+} -dependent ATPase and Na^+ , K^+ ATPase. Dicofol inhibits all three ATPases. Most of these acaricides were less active than DDT as inhibitors of oligomycin-sensitive Mg^{2+} -dependent ATPase but tetradifon was the most active and specific inhibitor of this enzyme tested. Chlorfenethol, chlorbenside, and ovex were poorer inhibitors of spider

mite ATPases than fish or insect ATPases but were more specific for Mg^{2+} ATPase in spider mites (58-61). Chlorophyllase activity and chlorophyll degradation in apple leaves were stimulated by dicofol, tetradifon, ovex, and Sulphenone (62). Subtoxic concentrations of dicofol inhibited vaccini virus replication in human Chang-strain liver cells and stimulated the replication of poliovirus (63). Tetrasul increased the weight of rat thyroid in 2-yr chronic feeding tests. In short-term experiments, the uptake of ^{131}I appeared to be higher with increasing dosages of tetrasul. A working hypothesis was proposed that tetrasul competes with thyroxine for protein-binding sites (64). Although any relationships of these activities to the primary mode and specificities of action of the bridged diphenyl acaricides remain unclear, they more clearly may have toxicological or environmental residue implications.

Summary

The bridged diphenyl acaricides exhibit remarkable properties of specificity, being particularly toxic to phytophagous mites but of very low toxicity to insects and mammals. Although many important facets of their broad mode of action are understood, virtually nothing is known of their primary mode of action or the underlying bases of their specificities. In most ways they are model compounds for integrated control and pest management activities. Because of these remarkable properties, they merit much greater attention and research effort than they have received to elucidate the fundamental and underlying bases involved.

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